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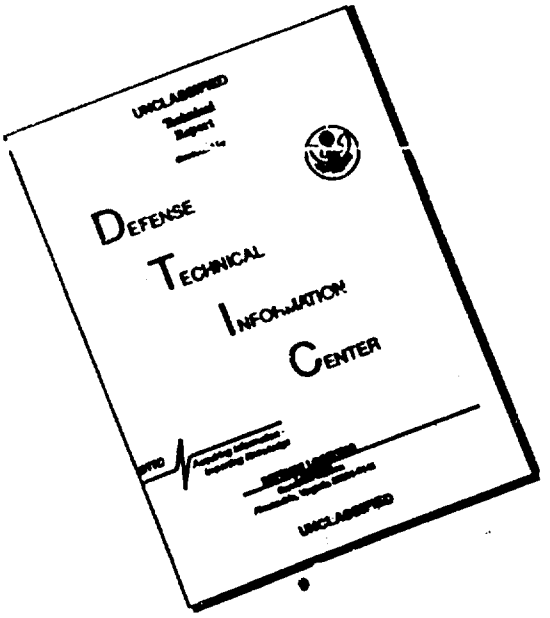

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Disturbance in the Central Respiratory Control during Botulinal Intoxication

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Although the toxin of the botulinal rod is one of the violent bacterial toxins that change strikingly the nature of the respiratory movements in man and in animals (2, 5 to 8, etc.), yet the mechanism of its action on the respiratory control is still largely unknown.

An assumption was expressed - though based on indirect evidence - that the respiratory disorder resulting from botulism is combined with the effects of toxin on myoneural connections of respiratory muscles (10).

We indicated previously (1) that the respiratory paralysis resulting from botulinal intoxication is not combined with the disturbance in the diaphragm function, as the data of some authors imply (10,11), but with the injury of the respiratory center. A fairly large experimental material had been accumulated up to the present time indicating that the medullary and respiratory center

possess a rhythmic activity, i.e. a capability of passing into a stage of stimulation.

Many researchers think that the reticular structure of myelencephalon includes, in addition to the rhythmic activity,

Figure 1 - Recording of respiratory movements and action potentials on the central end of the right diaphragmatic nerve in a rabbit. A - after 1 hour up to the cessation of spontaneous respiration; B - after 30 minutes following the cessation of spontaneous respiration. Legend above and below: respiratory movements, recording time 3 seconds; action potentials, recording time 0.02 seconds.

also the coordination (integration) activity. This opinion is verified by the fact that an integrated inspiratory event may be caused by a stimulation of a small area that is considered to be a tonic inspiratory center (15). Many investigations disclosed (12, 13, 15,

16, 18) that some chemical substances can exert separate effects on the rhythmic activity of the respiratory center and on the coordination activity.

We studied in the current work the effects of botulinal toxin on single central components of the respiratory control, i.e. on the rhythmic and coordination activities of the respiratory center.

The experiments were conducted on 34 rabbits and cats, each weighing from 2 to 3 kg. The animals were administered botulinal toxin type A in 1 to 2 mg/kg dose (obtained from N.F.GAMALEI'S Institute of Epidemiology and Microbiology; 1 mg contained 500 Dlm for a mouse for intravenous administration). The recording of respiratory movements in animals was accomplished with the aid of a (pulse) rubber cuff applied to the chest. We used urethan (intra-abdominally 1.2 gm/kg) as a narcotic.

In order to examine the rhythmic activity of inspiratory neurons in the respiratory center, we recorded the action potentials of 1 or 2 fibers of the diaphragmatic nerve. The action potentials were picked up on the central end of the nerve with the aid of platinum electrodes under paraffin oil, according to the method described by several authors (14, 17, 19, 20).

As the next proceeding to study the coordination activity of the respiratory center, we performed an operation exposing the myelencephalon. The stimulation was accomplished with the aid of steel bipolar electrodes connected to the electric stimulator of the Grakh-1 type. The position of the electrodes was determined with the Hartley-Clark stereotaxic apparatus. The electrodes were

placed 2.5 mm deep, laterally from the center line to 1.5 mm, and 2 mm upward from both. The stimulation was produced with electric current of diverse voltage, at 55 cps frequency and with 0.2 m/sec of pulse duration. The stimulation time equalled 6 to 8 seconds after interval of 10 to 15 minutes.

Following the administration of toxin, we examined the general symptoms of toxic effects in 10 animals not anesthetized. With the intravenous administration of 10 to 15 gm of dry toxin (5,000 to 10,000 Dlm for mice), the following symptoms developed in rabbits and cats: adynamia, paresis of extremities, mydriasis, refusal of food, muscle tremor in extremities and in the neck. Rabbits died after 3 to 4 hours, and cats after 6 to 7 days. Changes in the respiration appeared in rabbits after 30 to 40 minutes following the administration of toxin. At first, we observed a brief deepness and increased frequency in respiratory movements; later, as the respiratory frequency decreased slightly, the amplitude of respiratory movements diminished. Single, deep inspirations were often recorded on a phon during shallow breathing. In last minutes of their life, the respiration of rabbits always resembled gasping. The respiratory disturbances in cats appeared on the fourth day after administration of toxin. Later, the administration of toxin caused disorders in the respiration, in respiratory control and also the appearance of pathological respiratory patterns that were combined with changes in the amplitude of respiratory movements.

In order to clarify the question whether botulinal toxin affects the rhythmic activity of the respiratory center, we conducted

10 experiments on rabbits and cats, recording the action potentials on the central end of the diaphragmatic nerve during spontaneous and artificial respirations. We observed in healthy cats and rabbits discharges of low frequency during the entire or partial phase of

Figure 2 - Inspiratory reaction after stimulation of the ventrimesal region of myelencephalon in a rabbit. A and B - 2 hours after administration of botulinal toxin and application of 0.2 volts stimulation; C and D - 2½ hours after administration of botulinal toxin and application of 0.35 volts stimulation. Legend above and below: respiratory movements and recording of stimulation (figures indicate voltage); recording time 3 seconds.

expiration. Then, as discharge became accelerated, a burst of high frequency pulses followed at the time of inspiration. With the administration of toxin, the low frequency discharges during expiration and also the duration and the frequency mean decreased, thus concurring with the inspirational emission in the diaphragmatic nerve. However, rhythmic respiratory pulses occurred during 1½ to 2 hours in all experiments after cessation of spontaneous

breathing on a phon in the course of artificial respiration and during its brief switched-off period (figure 1).

Therefore, the botulinal toxin does not primarily affect the rhythmic activity of the respiratory center.

In order to investigate the coordination (integration) activity of the respiratory center, we conducted experiments on 9 rabbits, using stimulation of electric current of diverse voltage in the ventromedian region of the brain stem. As a power stimulation threshold we defined the inspiratory response observed with the least interrupted rhythm.

Figure 2 shows changes in the power stimulation threshold in the presence of constant frequency, as observed in a rabbit after administration of 2 mg/kg of toxin.

The botulinal toxin slightly increased the power stimulation threshold for development of a constant apnea and it decreased noticeably the amplitude of inspiratory reactions. After administration of the toxin, also a decrease in the amplitude of inspiratory reactions was clearly expressed in a rabbit (figure 3). It is interesting that the amplitude of inspiratory responses in rabbits decreased gradually during artificial respiration prior to and after the cessation of spontaneous respiratory movements.

The involvement of the expiratory activity by botulinal toxin in a part of the brain stem was determined by experimentations (5 experiments) and studies of the cough reaction produced by a mechanical stimulation in tracheal mucosa of cats with botulinal intoxication. It is obvious from figure 4 that, as the intoxication

increased, the cough response to the stimulation of trachea decreased

Figure 3 - Inspiratory reaction during stimulation of the ventromedian region in the brain stem of a rabbit in various periods after administration of botulinal toxin (experiment on October 27, 1959). A - prior to administration of the toxin; B- after 30 minutes; C - after 1 hour; D - after 1½ hours following the administration of botulinal toxin. Legend the same as in figure 2.

Figure 4 - Cough reflex in a cat during botulinal intoxication. A - after 8 hours following the administration of botulinal toxin; B - on the 4th day after administration botulinal toxin (experiment on October 30, 1959).

Therefore, the botulinal toxin affects the coordination activity (inspiratory and expiratory tonic functions) in a part of the brain stem, but does not influence its rhythmical activity.

It has been determined that the objective of the action of

bacterial toxins could be numerous links of the control of neural functions (3, 4). The analysis of the paralysing effect of botulinal toxin on respiration proved that, due to the effects of the toxin, inhibition is imposed on the side of the coordination (integration) activity of the respiratory center, but the toxin has no significant effect on the rhythmic activity of the brain stem. The botulinal toxin decreases the amplitude of respiratory reactions after electric stimulation in the ventromedian region of the brain stem and hardly changes the power stimulation threshold for development of a constant apnea. The investigation of cough reactions in cats at various periods of intoxication indicated that botulinal toxin affects the expiratory activity of the brain stem. The above data fully agree with the clinical observations and show that botulism patients are either able to cough with difficulty, or not at all (6).

Conclusions

1. The botulinal toxin caused a progressive decline in the amplitude of inspiratory reactions following electrical stimulation in the ventromedian region of the brain stem prior to and after the cessation of respiratory movements.

2. With the cessation of spontaneous respiration on a phon in the course of artificial respiration in animals affected with botulinal intoxication, we recorded for several hours the action potentials from the respiratory center.

3. The botulinal toxin caused an inhibition of the coordination (integration) activity of the respiratory center without showing any significant effect on the rhythmic respiratory activity.

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Summary (copy)

To study functional disturbances of central portions of the nervous regulation of respiration in botulin intoxication, the

rhythmic and coordination activity of medullary respiratory centre was investigated in rabbits and cats. The paralysing effect of botulin on respiration was analysed by stimulating the ventramedial area of the brain stem by means of electric current and by eliminating the action potentials from the central and of the phrenic nerve. This toxin inhibited the coordination activity of respiratory centre and produced no significant effect on the rhythmic activity.